Oncogene Surveillance: Differential role of Runx3 and p53

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RUNX family are evolutionarily conserved metazoan genes that encode a DNA binding subunit of a transcription factor. Recently, RUNX gene along with p53 and other transcription factors were found to be present in unicellular organism considered as a precursor to the metazoan. RUNX is known to function in cell specification in development and frequently involved in carcinogenesis. We reported earlier that Runx3 functions as a barrier to gastric and colon carcinogenesis (1,2). More recently, we began analyzing the K-Ras-induced lung cancer using mouse model.

In an attempt to cure cancer by restoration of p53, two groups performed sophisticated mouse studies using K-Ras-induced lung adenocarcinoma. The results reported in 2010 indicated that p53 destroyed only high-grade adenocarcinoma but not adenoma (3,4). If p53 is entirely responsible for oncogene surveillance, the results described in these two papers are puzzling.

We used mice carrying $Runx3^{f/f}$, $K\text{-}Ras^{LSL\text{-}G12D}$, Adeno-Cre or tm/CreERT in different combinations and conditionally activated Cre recombinase by two different methods: one is to express in a large number of lung cells, the other in much smaller number of cells. We found that $K\text{-}Ras^{G12D}$ alone induced lung adenocarcinoma when Cre was activated in a large number of cells. However, If Cre was activated in a small number of cells, activation of $K\text{-}Ras^{G12D}$ alone or inactivation of Runx3 alone did not induce any tumor over one year. Only when Cre was activated in a small number of cells in the mouse carrying $K\text{-}Ras^{G12D}$, $Runx3^{f/f}$, lung adenocacinoma developed very rapidly, indicating that inactivation of Runx3 is required for K-Ras to induce adenocarcinoma.

We analyzed the possible mechanism for this phenomenon and the results will be presented. This study suggested that first line of defense against tumor formation is carried out by Runx3 and the second line by p53.

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POSITIONS AND HONORS

1968	Kuroya Award (Japanese Society for Microbiology)
1995	Princess Takamatsu Cancer Research Award
2003	Tomizo Yoshida Prize (Japanese Cancer Association)
2010	President's Science Awards (2010) --- (A*STAR, Singapore)

RECENT PUBLICATIONS

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